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ABSTRACT:

The present invention is drawn to a pharmaceutical composition characterized by containing a composition (A) which contains pitavastatin, a salt thereof, or an ester thereof and which initiates release thereof at least in the stomach, and an enteric composition (B) which contains pitavastatin, a salt thereof, or an ester thereof. By use of the controlled release pharmaceutical composition of the present invention, the blood level of pitavastatin can be maintained at an appropriate level immediately after administration over a long period of time. Thus, highly safety and effective treatment of hypercholesterolemia can be performed.

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Abstract Paragraph:
The present invention is drawn to a pharmaceutical composition characterized by containing a composition (A) which contains pitavastatin, a salt thereof, or an ester thereof and which initiates release thereof at least in the stomach, and an enteric composition (B) which contains pitavastatin, a salt thereof, or an ester thereof. By use of the controlled release pharmaceutical composition of the present invention, the blood level of pitavastatin can be maintained at an appropriate level immediately after administration over a long period of time. Thus, highly safety and effective treatment of hypercholesterolemia can be performed.

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Summary of Invention Paragraph:
[0001] The present invention relates to a controlled release pharmaceutical composition containing pitavastatin, which is an HMG-CoA reductase inhibitor, a salt thereof, or an ester thereof.

Summary of Invention Paragraph:
[0002] Pitavastatin and salts and esters thereof are known to be useful as drugs for treating hypercholesterolemia, by virtue of their excellent HMG-CoA reductase inhibitory activity (U.S. Pat. No. 5,856,336 and EP 0,304,063). Hypercholesterolemia treatment drugs such as the pitavastatin-containing drugs are used in the form of peroral preparations such as tablets, granules and capsules (U.S. Pat. No. 6,465,477 and WO 97/23200). In general, peroral drug preparations are designed such that the blood level of the active ingredient reaches its peak 0.5 to 3 hours after ingestion, and the level rapidly decreases afterward. However, since cholesterol is synthesized in the body during the period from midnight to morning, it is highly likely that blood level of the active ingredient does not match the time at which biosynthesis of cholesterol occurs.

Summary of Invention Paragraph:
[0003] Although pitavastatin and salts and esters thereof are also known to exert high activity and have high safety, an excessively high blood level thereof is not preferred, from the viewpoint of prevention against the side effects.

Summary of Invention Paragraph:
[0004] In addition, it is also desired for pitavastatin and salts and esters thereof to maintain an excellent hypercholesterol-reducing action for a long period of time.

Summary of Invention Paragraph:
[0005] In view of the foregoing, an object of the present invention is to provide a controlled release pharmaceutical composition which can reliably maintain an appropriate blood level of pitavastatin, a salt thereof, or an ester thereof over a long period of time.

Summary of Invention Paragraph:
[0006] The present inventors have carried out extensive studies in order to develop a controlled release pharmaceutical composition containing pitavastatin, a salt thereof, or an ester thereof. A first approach to resolution of the aforementioned problems is a sustained release drug preparation exhibiting zero-order drug release. However, when such a sustained release drug preparation exhibiting zero-order drug release is administered singly, increasing the blood level thereof immediately after administration is difficult, resulting in a considerably low level of the maximum blood concentration (C.sub.max) as compared with ordinary drug preparations of the same dose. In addition, the area under the blood concentration curve (AUC)--an index of hypercholesterol-reducing action--decreases considerably. Thus, the first approach fails to resolve the aforementioned problems.

Summary of Invention Paragraph:
[0007] Consequently, the present inventors have studied the absorption kinetics of pitavastatin and salts and esters thereof, and have found that pitavastatin and salts and esters thereof are absorbed most effectively in the duodenum and also effectively in the large intestine as well as the small intestine, which contrasts greatly with the general tendency for ordinary drugs to be absorbed in the small intestine. On the basis of this finding, the present inventors have conducted further studies, and have found that when a drug preparation is formed from a composition which contains pitavastatin, a salt thereof, or an ester thereof and which initiates release thereof at least in the stomach and, in combination, an enteric composition which contains pitavastatin, a salt thereof, or an ester thereof, the drug preparation can attain an appropriate effective blood level thereof immediately after administration and can maintain such an appropriate blood level for a long period of time. The present invention has been accomplished on the basis of these findings.

Summary of Invention Paragraph:
[0008] Accordingly, the present invention provides a pharmaceutical composition characterized by comprising a composition (A) which contains pitavastatin, a salt thereof, or an ester thereof and which initiates release thereof at least in the stomach, and an enteric composition (B) which contains pitavastatin, a salt thereof, or an ester thereof.

Brief Description of Drawings Paragraph:
[0010] FIG. 2 shows the change in blood plasma level of pitavastatin in the case where pitavastatin was perorally administered in dogs, in the form of the compositions of Example 5 and Comparative Examples 1 and 2.

Detail Description Paragraph:
[0011] The characteristic feature of the pharmaceutical composition of the present invention is that the composition comprises a composition (A) which contains pitavastatin, a salt thereof, or an ester thereof (hereinafter these compounds are collectively referred to as pitavastatin) and which initiates release of pitavastatin at least in the stomach, and an enteric composition (B) which contains pitavastatin. Herein, the composition (A) initiates release of pitavastatin at least in the stomach. The composition (A) may release, in the stomach, the practical portion of pitavastatin or a portion of pitavastatin. However, a composition (A) which releases at least 30 mass % pitavastatin in the stomach is preferred, from the viewpoint of reliable attainment of an effective blood level of pitavastatin immediately after administration.

Detail Description Paragraph:
[0012] Preferably, the enteric composition of (B) is a composition prepared by coating pitavastatin or a pitavastatin-containing composition with a component which dissolves at a pH of 3.0 or higher. Alternatively, a composition prepared by mixing pitavastatin with a component which dissolves at a pH of 3.0 or higher is preferred for the enteric composition of (B). Accordingly, the portion of

pitavastatin contained in the enteric composition (B) is hardly released in the stomach but is released after passing through the near area of the duodenum.

Detail Description Paragraph:
[0013] One characteristic of pitavastatin, which serves an active ingredient of the controlled release pharmaceutical composition in the present invention, is high absorption thereof in the duodenum (see Table 1). Thus, the practical portion of pitavastatin released from the composition (A) in the stomach is considered to be absorbed in the duodenum. In contrast, the enteric composition (B) releases pitavastatin after passing through the near area of the duodenum. Thus, pitavastatin released from the composition (B) is firstly absorbed in the small intestine. The percentage of pitavastatin absorption in the small intestine is about one-third that in the duodenum (see Table 1). Therefore, even if pitavastatin is rapidly released in the small intestine, the abrupt absorption of pitavastatin does not occur. Furthermore, pitavastatin requires a relatively long period of time for the passage thereof through these organs. Thus, pitavastatin is slowly absorbed in sites; i.e., from the small intestine to the large intestine, over a relatively long time. Therefore, the controlled release pharmaceutical composition of the present invention can maintain a desirable blood level of pitavastatin.

Detail Description Paragraph:
[0014] Since the absorption site in digestive tract of ordinary drugs is the small intestine, a drug which has passed through the small intestine and has reached the large intestine is hardly absorbed. In this connection, sustained release drug preparations involve a problem, for example, in that bioavailability of the drug is reduced as compared with ordinary drug preparations of the same dose. In contrast, pitavastatin exhibits high absorption in the large intestine as well as in the duodenum (see Table 1). Therefore, the controlled release pharmaceutical composition of the present invention can attain a virtually identical level of bioavailability as compared with ordinary drug preparations of the same dose.

Detail Description Paragraph:
[0015] Pitavastatin which is used in the controlled release pharmaceutical composition of the present invention is a compound denominated (+)-(3R,5S,6E)-7-[2-cyclopropyl-4-(4-fluorophenyl)-3-quinolyl]-3,5-dihydr- oxy-6-heptenoic acid. As mentioned above, the compound is known to be an excellent HMG-CoA reductase inhibitor and to be useful as a drug for treating hypercholesterolemia. Examples of preferred pitavastatin salts includes salts of alkali metal (e.g., sodium or potassium) and salts of alkaline earth metal (e.g., calcium or magnesium). Of these, calcium salt is particularly preferred. Examples of preferred pitavastatin esters include alkyl esters such as a methyl ester, an ethyl ester, an i-propyl ester, and an n-propyl ester.

Detail Description Paragraph:
[0016] As mentioned above, the composition (A) preferably releases in the stomach at least 30 mass % pitavastatin contained in the composition (A). More preferably, the amount of pitavastatin released in the stomach is controlled such that the composition (A) releases, in the stomach, for example, at least 30 mass % and less than 60 mass % pitavastatin, at least 60 mass % and less than 85 mass % pitavastatin, at least 85 mass % pitavastatin contained in the composition (A). Herein, the percentage of pitavastatin release from the composition (A) in the stomach is determined in accordance with General Test Methods in Japanese Pharmacopoeia, Dissolution Test Method No. 2 (Paddle method). Specifically, the composition (A) to be tested is added to artificial gastric juice medium (pH: 1.2; 900 mL), and the medium is stirred for 30 minutes at 37.+-.1.degree. C. with a paddle rotation of 100 rpm. After termination of stirring, the amount of pitavastatin dissolved in artificial gastric juice medium is determined. Alternatively, in accordance with General Test Methods in Japanese Pharmacopoeia, Dissolution Test Method No. 2 (Paddle method), a pharmaceutical composition to be tested is added to artificial gastric juice medium (pH: 1.2; 900 mL), and the

medium is stirred for 30 minutes at 37.+-.1.degree. C. with a paddle rotation of 100 rpm. After termination of stirring, the amount of pitavastatin dissolved in artificial gastric juice medium is determined. The percentage of pitavastatin release from the composition (A) is determined through calculation by use of the amount of pitavastatin contained the composition (A) included in the pharmaceutical composition to be tested.

Detail Description Paragraph:
[0017] The percentage of pitavastatin release from the composition (A) in the stomach can be regulated by adding a sustained release component to an ordinary employed base. Examples of the bases which can be incorporated into the composition (A) include diluents such as lactose, corn starch, modified corn starch, mannitol, sorbitol, wood cellulose, microcrystalline cellulose, and calcium carbonate; binders such as hydroxypropyl cellulose, hydroxypropylmethyl cellulose, polyvinylpyrrolidone, and partially hydrolyzed polyvinyl alcohol; disintegrants such as low-substituted hydroxypropyl cellulose, carmellose, sodium carboxystarch, carmellose calcium, corn starch, partial pregelatinized starch, croscarmellose sodium, and crospovidone; lubricants such as magnesium stearate, stearic acid, palmitic acid, calcium stearate, talc; coating agents such as saccharides, cellulose derivatives, polyvinyl derivatives, alkylene oxide polymers, greases, methyl methacrylate.butyl methacrylate.dimethylaminoethyl methacrylate copolymers, acacia, locust bean gum, carrageenan, xanthan gum, pregelatinized starch, pectin, glucomannan, gluten, casein, gelatin, and zein.

Detail Description Paragraph:
[0019] Examples of the cellulose derivatives include methylcellulose, ethylcellulose, hydroxypropylcellulose, hydroxypropylmethylcellulose, and low-substituted hydroxypropylcellulose.

Detail Description Paragraph:
[0021] Examples of the alkylene oxide polymers include polyethylene glycol and polypropylene glycol.

Detail Description Paragraph:
[0023] In order to enhance the time-lapsing stability of pitavastatin, a basic substance which can elevate pH of an aqueous solution or dispersion of the composition (A) to 6.8 or higher, particularly 6.8 to 7.8 is preferably added to the composition (A). Examples of such basic substances include antacids such as magnesium aluminometasilicate, magnesium aluminosilicate, magnesium aluminate, dried aluminum hydroxide, synthetic hydrotalcite, synthetic aluminum silicate, magnesium carbonate, precipitated calcium carbonate, magnesium oxide, aluminum hydroxide, and sodium hydrogencarbonate; and pH-adjuster agent such as L-arginine, sodium phosphate, disodium hydrogenphosphate, sodium dihydrogenphosphate, potassium phosphate, dipotassium hydrogenphosphate, potassium dihydrogenphosphate, disodium citrate, sodium succinate, ammonium chloride, and sodium benzoate. Among them, magnesium aluminometasilicate, L-arginine, and dipotassium hydrogenphosphate are particularly preferably used.

Detail Description Paragraph:
[0025] Preferably, the sustained release component is incorporated into the composition (A) in such a manner that pitavastatin or a pitavastatin-containing composition is coated with the sustained release component, or that pitavastatin and the sustained release component are mixed. Examples of the sustained release components for coating include biodegradable polymers, cellulose derivatives, (meth)acrylic acid (co)polymers, alkylene oxide polymers, greases, silicones, chitin, chitosan, casein, tragacanth gum, guar gum, gellan gum, and acacia.

Detail Description Paragraph:
[0027] Examples of the cellulose derivatives include methylcellulose, ethylcellulose, propylcellulose, hydroxymethylcellulose, hydroxyethylcellulose,

hydroxypropylcellulose, hydroxypropylmethylcellulo- se, carboxymethylcellulose, carboxyethylcellulose, carboxypropylcellulose, methylhydroxypropylcellulose, cellulose acetyl phthalate, cellulose diacetyl phthalate, cellulose triacetyl phthalate, polyoxyethylcellulose phthalate, hydroxyethylcellulose phthalate, hydroxypropylcellulose phthalate, cellulose acetate, and salts thereof.

Detail Description Paragraph:
[0029] Examples of the alkylene oxide polymers include polyethylene glycol and polypropylene glycol.

Detail Description Paragraph:
[0032] Examples of the sustained release components to be mixed include biodegradable polymers, starches, dextrans, cellulose derivatives, (meth)acrylic acid (co)polymers, alkylene oxide polymers, greases, carrageenan, chitin, chitosan, casein, tragacanth gum, guar gum, gellan gum, paraffin, silicones, acacia, poly (glutamic acid), poly(aspartic acid), polylysine, polyarginine, alginic acid, pectic acid, and xanthan gum.

Detail Description Paragraph:
[0038] Examples of the alkylene oxide polymers include polyethylene glycol and polypropylene glycol.

Detail Description Paragraph:
[0041] The enteric composition (B) is preferably obtained by coating pitavastatin or a pitavastatin-containing composition with a component which dissolves at a pH of 3.0 or higher, preferably 4.0 or higher, more preferably 5.0 or higher, or by mixing pitavastatin with a component which dissolves at a pH of 3.0 or higher, preferably 4.0 or higher, more preferably 5.0 or higher. Examples of the components which dissolve at a pH of 3.0 or higher include enteric cellulose derivatives, enteric (meth)acrylic acid (co)polymers, enteric maleic acid copolymers, and enteric polyvinyl derivatives. Notably, these components which dissolve at a pH of 3.0 or higher must have no solubility in artificial gastric juice medium having a pH of 1.2.

Detail Description Paragraph:
[0046] To the enteric composition (B), there may be further added any of the sustained release components, diluents, binders, disintegrants, lubricants, and basic substances, which are described in relation to the components which can be incorporated into the aforementioned composition (A).

Detail Description Paragraph:
[0047] The controlled release pharmaceutical composition of the present invention comprises the composition (A) and the enteric composition (B). The ratio by mass of pitavastatin contained in the composition (A) to pitavastatin contained in the enteric composition (B) is adjusted such that the C.sub.max of pitavastatin upon peroral administration of the controlled release pharmaceutical composition of the present invention, and can be appropriately controlled; such that reduction in AUC can be prevented; and such that a constant blood level of pitavastatin can be attained over a long period of time. As used herein, the term "appropriately controlled C.sub.max" refers to a maximum blood level of pitavastatin which is obtained when a composition (A) containing 1 to 8 mg of pitavastatin without sustained release component is perorally administered to a human subject.

Detail Description Paragraph:
[0048] The mass ratio of pitavastatin contained in the composition (A) to pitavastatin contained in the enteric composition (B) varies in accordance with the percentage of release of pitavastatin from the composition (A) in the stomach. When the percentage of release is 85 mass % or more, the preferable ratio is within a range of 1:1 to 1:40, more preferably 1:1 to 1:20, particularly preferably 1:1 to 1:7. When the percentage of release is at least 60 mass % and less than 85 mass %,

the preferable ratio is within a range of 15:1 to 1:30, more preferably 10:1 to 1:20, particularly preferably 5:1 to 1:15. When the percentage of release is at least 30 mass % and less than 60 mass %, the preferable ratio is within a range of 30:1 to 1:20, more preferably 20:1 to 1:15, particularly preferably 15:1 to 1:10.

Detail Description Paragraph:
[0051] No particular limitation is imposed on the amount of pitavastatin incorporated into the controlled release pharmaceutical composition of the present invention, and the preferable amount is within a range of 0.01 to 60 mass %.

Detail Description Paragraph:
[0052] The amounts of ordinary bases, sustained release components, and enteric components incorporated into the controlled release pharmaceutical composition of the present invention vary depending on the types of these additives, design of release control of drugs, etc. However, the amount of each additive preferably is within a range of 0.01 to 80 mass %, more preferably 0.1 to 50 mass %, particularly preferably 1.0 to 30 mass %.

Detail Description Paragraph:
[0054] Examples of preferred drug forms of the controlled release pharmaceutical composition of the present invention for attaining a satisfactory blood level of pitavastatin include the following forms:

Detail Description Paragraph:
[0065] The daily dose of pitavastatin contained in-the thus-obtained controlled release pharmaceutical composition of the present invention is adjusted to 0.5 to 64 mg, preferably 1 to 32 mg, particularly preferably 4 to 16 mg.

Detail Description Paragraph:
[0068] To purified water (3000.0 g), pitavastatin calcium salt (240.0 g), sucrose (615.0 g), hydroxypropylmethylcellulose (registered trade mark: TC-5R) (360.0 g), magnesium alumino metasilicate (48.0 g), talc (12.0 g) and triethyl citrate (45.0 g) were added, and these components were dissolved/dispersed by use of a disperser, to thereby prepare a drug-containing coating solution.

Detail Description Paragraph:
[0072] To purified water (1000.0 g), pitavastatin calcium salt (80.0 g), sucrose (205.0 g), hydroxypropylmethylcellulose (registered trade mark: TC-5R) (120.0 g), magnesium alumino metasilicate (16.0 g), talc (4.0 g) and triethyl citrate (15.0 g) were added, and these components were dissolved/dispersed by use of a disperser, to thereby prepare a drug-containing coating solution.

Detail Description Paragraph:
[0078] To purified water (500.0 g), pitavastatin calcium salt (40.0 g), sucrose (102.5 g), hydroxypropylmethylcellulose (registered trade mark: TC-5R) (60.0 g), magnesium alumino metasilicate (8.0 g), talc (2.0 g) and triethyl citrate (7.5 g) were added, and these components were dissolved/dispersed by use of a disperser, to thereby prepare a drug-containing coating solution.

Detail Description Paragraph:
[0079] To ethanol (1312.5 g), hydroxypropylmethylcellulose phthalate (161.7 g), triethyl citrate (16.1 g) and talc (32.2 g) were added, and these components were dissolved/dispersed by use of a disperser, to thereby prepare an enteric coating solution.

Detail Description Paragraph:
[0081] To purified water (500.0 g), pitavastatin calcium salt (40.0 g), sucrose (102.5 g), hydroxypropylmethylcellulose (registered trade mark: TC-5R) (60.0 g), magnesium alumino metasilicate (8.0 g), talc (2.0 g) and triethyl citrate (7.5 g) were added, and these components were dissolved/dispersed by use of a disperser, to

thereby prepare a drug-containing coating solution.

Detail Description Paragraph:
[0085] Hydroxypropylmethylcellulose (registered trade mark: TC-5R) (325.0 g) was dissolved in purified water (1500 g) by use of a disperser. Ethylcellulose (100.0 g), triethyl citrate (32.5 g) and talc (82.5 g) were dissolved/dispersed in ethanol (4000.0 g) by use of a disperser. The two solutions were mixed, to thereby prepare a coating solution.

Detail Description Paragraph:
[0092] A pitavastatin calcium salt (60.0 g), ethyl acrylate.methyl methacrylate (chlorotrimethylammonio)ethyl methacrylate copolymer (registered trade mark: Eudragit RS) (982.8 g), lactose (655.2 g), low-substituted hydroxypropylcellulose (90.0 g) and magnesium alumino metasilicate (12.0 g) were mixed, to thereby prepare a uniform powder mixture. A suitable amount of ethanol was added thereto, and the resultant mixture was granulated by a high-shear granulator, to thereby produce a granular product (1800.0 g).

Detail Description Paragraph:
[0093] To ethanol (5225.5 g), hydroxypropylmethylcellulose acetate succinate (311.85 g), triethyl citrate (31.05 g) and talc (62.1 g) were added, and these components were dissolved/dispersed by use of a disperser, to thereby prepare an enteric coating solution.

Detail Description Paragraph:
[0104] The granular product A (900.0 g), the enteric granular product (1170.0 g), crystalline cellulose (2146.2 g), hydroxypropylmethylcellulos- e (registered trade mark: TC-5R) (147.0 g), low-substituted hydroxypropylcellulose (588.0 g) and magnesium stearate (58.8 g) were mixed and compressed, to thereby produce 10,000 tablets, each tablet having a weight of 501.0 mg.

Detail Description Paragraph:
[0107] Pitavastatin calcium salt (40.0 g), lactose (3450.0 g), low-substituted hydroxypropylcellulose (770.0 g), hydroxypropylmethylcell- ulose(registered trade mark: TC-5R) (88.0 g) and magnesium alumino metasilicate (8.0 g) were mixed, to thereby prepare a uniform powder mixture. A suitable amount of purified water was added thereto, and the resultant mixture was granulated by a high-shear granulator. The thus-obtained granular product was mixed with magnesium stearate (44.0 g), to thereby produce a mixed granular product (4400.0 g).

Detail Description Paragraph:
[0112] A mixture containing the granular product A (600.0 g), crystalline cellulose (438.0 g), hydroxypropylmethylcellulose (registered trade mark: TC-5R) (30.0 g), low-substituted hydroxypropylcellulose (120.0 g) and magnesium stearate(12.0 g), and another mixture containing the enteric granular product A (780.0 g), crystalline cellulose (569.4 g), hydroxypropylmethylcellulose (registered trade mark: TC-5R) (39.0 g), low-substituted hydroxypropylcellulose (156.0 g) and magnesium stearate (15.6 g) were compressed, to thereby produce 10,000 two-layer tablets, each tablet having a weight of 276.0 mg (A layer: 120.0 mg, B layer: 156.0 mg).

Detail Description Paragraph:
[0115] Pitavastatin calcium salt (80.0 g), carboxymethylethylcellulose (1010.4 g), lactose (673.6 g), low-substituted hydroxypropylcellulose (200.0 g) and magnesium alumino metasilicate (16.0 g) were mixed, to thereby prepare a uniform powder mixture. A suitable amount of ethanol was added thereto, and the resultant mixture was granulated by a high-shear granulator. The thus-obtained granular product was mixed with magnesium stearate (20.0 g), to thereby produce an enteric mixed granular product (2000.0 g).

Detail Description Paragraph:
[0118] Pitavastatin calcium salt (80.0 g), ethyl acrylate.methyl methacrylate.(chlorotrimethylammonio)ethyl methacrylate copolymer (registered trade mark: Eudragit RS) (568.8 g), lactose (1603.2 g), low-substituted hydroxypropylcellulose (120.0 g) and magnesium alumino metasilicate (16.0 g) were mixed, to thereby prepare a uniform powder mixture. A suitable amount of ethanol was added thereto, and the resultant mixture was granulated by a high-shear granulator. The thus-obtained granular product was mixed with magnesium stearate (12.0 g), to thereby produce a mixed granular product (2400.0 g).

Detail Description Paragraph:
[0119] Pitavastatin calcium salt (40.0 g), carboxymethylethylcellulose (505.2 g), lactose (336.8 g), low-substituted hydroxypropylcellulose (100.0 g) and magnesium alumino metasilicate (8.0 g) were mixed, to thereby prepare a uniform powder mixture. A suitable amount of ethanol was added thereto, and the resultant mixture was granulated by a high-shear granulator. The thus-obtained granular product was mixed with magnesium stearate (10.0 g), to thereby produce an enteric mixed granular product (1000.0 g).

Detail Description Paragraph:
[0122] Pitavastatin calcium salt (60.0 g), lactose (324.0 g), low-substituted hydroxypropylcellulose (45.0 g), hydroxypropylmethylcellu- lose (registered trade mark: TC-5R) (7.5 g) and magnesium alumino metasilicate (9.0 g) were mixed, to thereby prepare a uniform powder mixture. A suitable amount of purified water was added thereto, and the resultant mixture was granulated by a high-shear granulator. The thus-obtained granular product and magnesium stearate (4.5 g) were mixed and compressed, to thereby produce 10,000 uncoated tablets (total 450.0 g), each tablet having a weight of 45.0 mg.

Detail Description Paragraph:
[0129] Pitavastatin calcium salt (90.0 g), methacrylate.methyl methacrylate copolymer (registered trade mark: Eudragit S) (380.7 g), lactose (253.8 g), low-substituted hydroxypropylcellulose (48.5 g) and magnesium alumino metasilicate (18.0 g) were mixed, to thereby prepare a uniform powder mixture. A suitable amount of ethanol was added thereto, and the resultant mixture was granulated by a high-shear granulator. The thus-obtained granular product and magnesium stearate (9.0 g) were mixed and compressed, to thereby produce 10,000 enteric tablets (800.0 g), each tablet having a weight of 80.0 mg.

Detail Description Paragraph:
[0132] To purified water (4000.0 g), pitavastatin calcium salt (120.0 g), sucrose (143.5 g), hydroxypropylmethylcellulose (registered trade mark: TC-5R) (84.0 g), magnesium alumino metasilicate (24.0 g), talc (6.0 g) and triethyl citrate (22.5 g) were added, and these components were dissolved/dispersed by use of a disperser, to thereby prepare a drug-containing coating solution.

Detail Description Paragraph:
[0136] The enteric granular product (1040.0 g), crystalline cellulose (759.2 g), hydroxypropylmethylcellulose (registered trade mark: TC-5R) (52.0 g), low-substituted hydroxypropylcellulose (208.0 g), and magnesium stearate (20.8 g) were mixed and compressed, to thereby produce 10,000 core tablets (2080.0 g), each tablet having a weight of 208.0 mg.

Detail Description Paragraph:
[0139] Pitavastatin-controlled-release tablets can be produced in accordance with the formulations shown in Table 15. Specifically, after preparation of core tablets, a drug-controlled-release coating layer is formed on the core tablets. Methacrylate.methyl methacrylate copolymer (trade name: Eudragit L, available from: Higuchi Inc.) is an enteric polymer which dissolves at a pH of 6 to 14, and ethylcellulose (trade name: Ethocel, product of Dow Chemical) is a sustained-

release polymer which is insoluble regardless of pH. The tablets obtained in Production Examples are pitavastatin-controlled-release tablets.

Detail Description Paragraph:
[0140] The tablets obtained in Production Example 1 are further coated with a pitavastatin-containing composition of Table 16. The tablet product of Example 14, which is formed of an outermost layer (immediately release portion) and an inner layer (controlled release portion) in combination, maintains reliable release of pitavastatin immediately after administration over a long period of time.

Detail Description Paragraph:
[0141] A pitavastatin-controlled-release granular product can be produced in accordance with the formulation shown in Table 17. Specifically, after preparation of core granules, a drug-controlled-release coating layer is formed on the core granules. The core granules and the drug-controlled-release-layer-coated core granules are mixed, to thereby yield a controlled release granular product.

Detail Description Paragraph:
[0143] A pitavastatin-controlled-release capsule product can be obtained by mixing core granules of Table 17; drug-controlled-release layer-coated granules of Table 17; and drug-controlled-release layer-coated granules of Table 18 and by charging the mixture in capsules.

Detail Description Paragraph:
[0144] A pitavastatin-controlled-release tablet product can be obtained by mixing core granules of Table 17; drug-controlled-release layer-coated granules of Table 17; and drug-controlled-release layer-coated granules of Table 18 and by compressed the mixture.

Detail Description Paragraph:
[0145] A pitavastatin-controlled-release multiple-layer tablet product can be obtained by individually compressing a layer of core granules of Table 17 and a layer of drug-controlled-release layer-coated granules of Table 17.

Detail Description Paragraph:
[0146] A pitavastatin-controlled-release tablet product can be produced in accordance with the formulation shown in Table 19. Specifically, after preparation of core tablets of Table 19, an outer layer component shown in Table 19 is formed on the core tablets by compressing, to thereby yield core-shell tablets.

Detail Description Paragraph:
[0149] Pitavastatin calcium salt (400.0 g), lactose (2160.0 g), low-substituted hydroxypropylcellulose (300.0 g), hydroxypropylmethylcell- ulose (registered trade mark: TC-5R) (50.0 g) and magnesium alumino metasilicate (60.0 g) were mixed, to thereby prepare a uniform powder mixture. Purified water (594.0 g) was added thereto, and the mixture was granulated by a high-shear granulator. The thus-obtained granular product and magnesium stearate (30.0 g) were mixed and compressed, to thereby produce 25,000 tablets, each tablet having a weight of 120.0 mg.

Detail Description Paragraph:
[0151] Pitavastatin calcium salt (320.0 g), lactose (960.0 g), hydroxypropylmethylcellulose (registered trade mark: Methocel K100LV) (1600.0 g), magnesium alumino metasilicate (128.0 g) and low-substituted hydroxypropylcellulose (160.0 g) were mixed, to thereby prepare a uniform powder mixture. Purified water (1108.8 g) was added thereto, and the resultant mixture was granulated by a high-shear granulator. The thus-obtained granular product and magnesium stearate (32.0 g) were mixed and compressed, to thereby produce 20,000 tablets, each tablet having a weight of 160.0 mg.

Detail Description Paragraph:
[0153] The dissolution property of pitavastatin from drug preparations; i.e., a drug preparation of Example 5 (composition (A) and enteric composition (B)); that of Comparative Example 1 (ordinary preparation); and that of Comparative Example 2 (sustained release preparation) was investigated in accordance with the following method.

Detail Description Paragraph:
[0157] Each of drug preparations of Example 5 and Comparative Examples 1 and 2 was added to the artificial gastric juice medium (900 mL) (pH: 1.2), and the medium was stirred at 37.+-.1.degree. C. with a paddle rotation of 100 rpm for three hours after starting of the test. Immediately thereafter, the dissolution test medium was changed to the artificial intestinal juice medium (900 mL) (pH: 6.8), and the dissolution test was continued for 21 hours at 37.+-.1.degree. C. with a paddle rotation of 100 rpm. The amount of dissolved drug was determined. A sample solution sampled at each timing was filtered by means of a membrane filter made of cellulose acetate (pore size: 0.45 .mu.m, DISMIC-25cs, product of Toyo Roshi), and the percent of dissolution of pitavastatin was determined with high performance liquid chromatography by use of a reverse-phase column (Develosil ODS-HG-5, product of Nomura Chemical). The results are shown in FIG. 1.

Detail Description Paragraph:
[0159] Each of the drug preparations prepared in Example 5, Comparative Example 1, and Comparative Example 2 was orally administered to an HRA beagle dog (body weight: about 10 kg) under fasting. After administration, blood was collected at different points in time for 24 hours, and the collected blood was subjected to centrifugation, whereby blood pitavastatin level was determined with high performance liquid chromatography. The results are shown in Table 22 and FIG. 2. The pharmacokinetic values are shown in Table 23. The results show that the controlled release drug preparation of the present invention reduces C.sub.max by 50% as compared with the ordinary drug preparation, while providing equivalent AUC comparable to that of the ordinary drug preparation. By contrast, in the case of the sustained release drug with zero-order release, C.sub.max and AUC are both significantly reduced as compared with the ordinary drug preparation. Therefore, the controlled release drug preparation of the present invention was found to be safe and highly effective.

Detail Description Paragraph:
[0161] By use of the controlled release pharmaceutical composition of the present invention, the blood level of pitavastatin can be maintained at an appropriate level immediately after administration over a long period of time. Thus, highly safety and effective treatment of hypercholesterolemia can be performed.

Detail Description Table CWU:
1TABLE 1 Absorption sites of pitavastatin in rat (in situ loop test) Absorption percentage (%) Sites 0.5 h 1 h Stomach 8.6 .+-. 1.1 14.4 .+-. 1.6 Duodenum 65.9 .+-. 2.1 60.3 .+-. 10.2 Small 23.1 .+-. 3.8 21.3 .+-. 3.0 intestine Large 34.4 .+-. 3.7 51.6 .+-. 6.7 intestine

Detail Description Table CWU:
2TABLE 2 Formulation Components (mg) Enteric Granular Purified sucrose spheres 114.00 granular product A Pitavastatin calcium salt 12.00 product A Sucrose 30.75 Hydroxypropylmethylcellulose 18.00 (Registered trade mark: TC-5R) Magnesium alumino metasilicate 2.40 Talc 0.60 Triethyl citrate 2.25 Subtotal 180.00 Methacrylate .multidot. methyl methacrylate 41.58 copolymer (Registered trade mark: Eudragit L) Talc 8.28 Triethyl citrate 4.14 Subtotal 234.00 Pitavastatin calcium salt 4.00 Sucrose 10.25 Hydroxypropylmethylcellulos- e (Registered trade 6.00 mark: TC-5R) Magnesium alumino metasilicate 0.80 Talc 0.20 Triethyl citrate 0.75 Total 256.00

Detail Description Table CWU:
3TABLE 3 Formulation Components (mg) Enteric Granular Granular product A 30.00 granular product Ethyl acrylate .multidot. methyl 12.40 product methacrylate .multidot. (chloro- trimethylammonio) ethyl methacrylate copolymer (Registered trade mark: Eudragit RS) Hydroxypropylcellulose 3.10 Talc 0.95 Triethyl citrate 1.55 Subtotal 48.00 Pitavastatin calcium salt 4.00 Sucrose 10.25 Hydroxypropylmethylcellul- ose (Registered 6.00 trade mark: TC-5R) Magnesium alumino metasilicate 0.80 Talc 0.20 Triethyl citrate 0.75 Hydroxypropylmethylcellulose phthalate 16.17 Talc 3.22 Triethyl citrate 1.61 Subtotal 91.00 Pitavastatin calcium salt 4.00 Sucrose 10.25 Hydroxypropylmethylcellulose (Registered trade 6.00 mark: TC-5R) Magnesium alumino metasilicate 0.80 Talc 0.20 Triethyl citrate 0.75 Total 113.00

Detail Description Table CWU:
4 TABLE 4 Formulation Components (mg) Granular Granular product A 180.00 product Ethylcellulose 10.00 Hydroxypropylmethylcellulose 32.50 (Registered trade mark: TC-5R) Talc 8.25 Triethyl citrate 3.25 Subtotal 234.00 Enteric Granular product A 60.00 granular Methacrylate .multidot. methyl methacrylate 13.86 product copolymer (Registered trade mark: Eudragit S) Talc 2.76 Triethyl citrate 1.38 Subtotal 78.00 Total 312.00

Detail Description Table CWU:
5TABLE 5 Formulation Components (mg) Granular product A 60.00 Granular Pitavastatin calcium salt 4.00 product Ethyl acrylate .multidot. methyl 65.52 methacrylate. (chlorotrimethylammonio)ethyl methacrylate copolymer (Registered trade mark: Eudragit RS) Lactose 43.68 Low-substituted hydroxypropylcellulose 6.00 Magnesium alumino metasilicate 0.80 Subtotal 120.00 Enteric Granular product A 90.00 granular Hydroxypropylmethylcellu- lose acetate 20.79 product succinate Talc 4.14 Triethyl citrate 2.07 Subtotal 117.00 Total 297.00

Detail Description Table CWU:
7TABLE 7 Formulation Components (mg) Granular product A 90.00 Enteric Granular product A 90.00 granular Methacrylate .multidot. ethyl acrylate copolymer 20.79 product (Registered trade mark: Eudragit L30D-55) Talc 4.14 Triehtyl citrate 2.07 Subtotal 117.00 Crystalline cellulose 214.62 Hydroxypropylmethylcellulose 14.70 (Registered trade mark: TC-5R) Low-substituted hydroxypropylcellulose 58.80 Magnesium stearate 5.88 Total 501.00

Detail Description Table CWU:
8TABLE 8 Formulation Components (mg) Enteric granular product A 195.00 Mixed Pitavastatin calcium salt 4.00 granular Lactose 345.00 product Low-substituted hydroxypropylcellulose 77.00 Hydroxypropylmethylcellulose 8.80 (Registered trade mark: TC-5R) Magnesium alumino metasilicate 0.80 Magnesium stearate 4.40 Subtotal 440.00 Total 635.00

Detail Description Table CWU:
9TABLE 9 Formulation Components (mg) A layer Granular product A 60.00 Crystalline cellulose 43.80 Hydroxypropylmethyl cellulose 3.00 (Registered trade mark: TC-5R) Low-substituted hydroxypropylcellulose 12.00 Magnesium stearate 1.20 Subtotal 120.00 B layer Enteric granular product A 78.00 Crystalline cellulose 56.94 Hydroxypropylmethylcellulose 3.90 (Registered trade mark: TC-5R) Low-substituted hydroxypropylcellulose 15.60 Magnesium stearate 1.56 Subtotal 156.00 Total 276.00

Detail Description Table CWU:
10TABLE 10 Formulation Components (mg) A layer Mixed granular product 440.00 B layer Pitavastatin calcium salt 8.00 Carboxymethylethylcellulose 101.04 Lactose 67.36 Low-substituted hydroxypropylcellulose 20.00 Magnesium alumino metasilicate 1.60 Magnesium stearate 2.00 Subtotal 200.00 Total 640.00

Detail Description Table CWU:

11TABLE 11 Formulation Components (mg) A layer Pitavastatin calcium salt 8.00 Ethyl acrylate .multidot. methyl methac- 56.88 rylate .multidot. (chlorotrimethylammonio) ethyl methacrylate copolymer (Registered trade mark: Eudragit RS) Lactose 160.32 Low-substituted hydroxypropylcellulose 12.00 Magnesium alumino metasilicate 1.60 Magnesium stearate 1.20 Subtotal 240.00 B layer Pitavastatin calcium salt 4.00 Carboxymethylethylcellulose 50.52 Lactose 33.68 Low-substituted hydroxypropylcellulose 10.00 Magnesium alumino metasilicate 0.80 Magnesium stearate 1.00 Subtotal 100.00 Total 340.00

Detail Description Table CWU:
12TABLE 12 Formulation Components (mg) Core Pitavastatin calcium salt 6.00 tablet Lactose 32.40 Low-substituted hydroxypropylcellulose 4.50 Hydroxypropylmethylcellulose 0.75 (Registered trade mark: TC-5R) Magnesium alumino metasilicate 0.90 Magnesium stearate 0.45 Methacrylate .multidot. methyl methacrylate copolymer 15.40 (Registered trade mark: Eudragit S) Talc 1.54 Triethyl citrate 3.06 Subtotal 65.00 Outer Mixed granular product 220.00 layer Total 285.00

Detail Description Table CWU:
13TABLE 13 Formulation Components (mg) Core Pitavastatin calcium salt 9.00 tablet Methacrylate .multidot. methyl methacrylate copolymer 38.07 (Registered trade mark: Eudragit S) Lactose 25.38 Low-substituted hydroxypropylcellulose 4.85 Magnesium alumino metasilicate 1.80 Magnesium stearate 0.90 Subtotal 80.00 Outer Mixed granular product 330.00 layer Total 410.00

Detail Description Table CWU:
14TABLE 14 Formulation Components (mg) Core Enteric Purified sucrose spheres 40.00 tablet granular Pitavastatin calcium salt 12.00 product Sucrose 14.35 Hydroxypropylmethylcellulose 8.40 (Registered trade mark: TC-5R) Magnesium alumino metasilicate 2.40 Talc 0.60 Triethyl citrate 2.25 Cellulose acetate phthalate 18.48 Talc 3.68 Triethyl citrate 1.84 Subtotal 104.00 Crystalline cellulose 75.92 Hydroxypropylmethylcellulose (Registered 5.20 trade mark: TC-5R) Low-substituted hydroxypropylcellulose 20.80 Magnesium stearate 2.08 Subtotal 208.00 Outer Mixed granular product 440.00 layer Total 648.00

Detail Description Table CWU:
15 TABLE 15 Production Examples (mg/T) Components 1 2 Core tablet Pitavastatin calcium salt 8.0 8.0 Lactose 94.4 94.4 Low-substituted hydroxypropylcel- 12.0 12.0 lulose Hydroxypropylmethylcellulose 2.0 2.0 Magnesium alumino metasilicate 2.4 2.4 Magnesium stearate 1.2 1.2 Subtotal 120.0 120.0 Drug-controlled- Methacrylate .multidot. methyl methacrylate 8.0 -- release coating copolymer layer Ethylcellulose -- 8.0 Triethyl citrate 1.2 1.2 Talc 2.5 2.5 Titanium oxide 1.3 1.3 Subtotal 13.0 13.0 Total 133.0 133.0

Detail Description Table CWU:
16 TABLE 16 Example 14 Components (mg/T) Inner Tablets (Production Example 1) 133.0 layer Outermost Pitavastatin calcium salt 8.0 layer Lactose 304.0 Low-substituted 36.0 hydroxypropylcellulose Hydroxypropylmethylcellulose 6.0 Magnesium alumino metasilicate 2.4 Magnesium stearate 3.6 Subtotal 360.0 Total 493.0

Detail Description Table CWU:
17 TABLE 17 Example 15 Components (mg/day) Core Pitavastatin calcium salt 8.0 granular D-mannitol 334.0 product Calcium Carboxymethylcellulose 21.0 Hydroxypropylcellulose 21.0 Magnesium alumino metasilicate 16.0 Subtotal 400.0 Drug- Methacrylate.methyl methacrylate 54.0 controlled- copolymer release Triethyl citrate 12.0 coating Talc 50.0 layer Titanium oxide 4.0 Subtotal 120.0

Detail Description Table CWU:
18 TABLE 18 Example 16 Components (mg/day) Core Pitavastatin calcium salt 8.0 granular D-mannitol 334.0 product Calcium Carboxymethylcellulose 21.0 Hydroxypropylcellulose 21.0 Magnesium alumino metasilicate 16.0 Subtotal 400.0

Drug- Methacrylate.methyl methacrylate 54.0 controlled- copolymer release Ethylcellulose 27.0 coating Triethyl citrate 18.0 layer Talc 75.0 Titanium oxide 6.0 Subtotal 180.0

Detail Description Table CWU:
19 TABLE 19 Production Example 3 Components (mg/T) Core Pitavastatin calcium salt 8.0 tablet Lactose 46.4 Crospovidone 20.0 Hydroxypropylmethylcellulose 2.0 Magnesium alumino metasilicate 2.4 Ethyl acrylate.methyl methacrylate. 20.0 (chlorotrimethylammonio)ethyl methacrylate copolymer*.sup.1 Monoglyceride 20.0 Magnesium stearate 1.2 Total 120.0 Outer Pitavastatin calcium salt 8.0 layer Lactose 304.0 Low-substituted 36.0 hydroxypropylcellulose Hydroxypropylmethylcellulose 6.0 Magnesium alumino metasilicate 2.4 Magnesium stearate 3.6 Subtotal 360.0 *.sup.1Eudragit RS sold by Higuchi Inc.

Detail Description Table CWU:
20 TABLE 20 Components Formulation (mg) Pitavastatin calcium salt 16.00 Lactose 86.40 Low-substituted hydroxypropylcellulose 12.00 Hydroxypropylmethylcellulos 2.00 (Registered trade mark: TC-5R) Magnesium alumino metasilicate 2.40 Magnesium stearate 1.20 Total 120.00

Detail Description Table CWU:
21 TABLE 21 Components Formulation (mg) Pitavastatin calcium salt 16.00 Lactose 48.00 Hydroxypropylmethylcellulose 80.00 (Registered trade mark: Methocel K100LV) Magnesium alumino metasilicate 6.40 Low-substituted hydroxypropylcellulose 8.00 Magnesium stearate 1.60 Total 160.00

Detail Description Table CWU:
22TABLE 22 Pitavastatin blood plasma level at each sampling time of the composition prepared in Example 5 and Comparative Examples 1 and 2 in beagle dog oral administration Time (h) 0 0.5 1 1.5 2 3 4 6 8 10 24 Ex. 5 0 229.7 505.7 533.3 536.3 386.0 373.0 229.3 112.5 59.8 8.2 (ng/mL) Comp. Ex. 1 0 1246.3 1179.7 690.8 475.2 323.7 226.5 155.8 49.3 29.0 8.3 (ng/mL) Comp. Ex. 2 0 10.2 52.2 73.7 76.5 131.3 161.8 171.7 49.0 25.3 3.2 (ng/mL)

CLAIMS:

1. A controlled release pharmaceutical composition characterized by comprising a composition (A) which contains pitavastatin, a salt thereof, or an ester thereof and which initiates release thereof at least in the stomach, and an enteric composition (B) which contains pitavastatin, a salt thereof, or an ester thereof.

2. A controlled release pharmaceutical composition as described in claim 1, wherein the composition (A) releases in the stomach at least 30 mass % pitavastatin, a salt thereof, or an ester thereof contained in the composition (A).

3. A controlled release pharmaceutical composition as described in claim 1, which has a ratio by mass of pitavastatin, a salt thereof, or an ester thereof contained in the composition (A) to pitavastatin, a salt thereof, or an ester thereof contained in the enteric composition (B) falling within a range of 30:1 to 1:40.

4. A controlled release pharmaceutical composition as described in claim 1, wherein the composition (A) releases in the stomach at least 85 mass % pitavastatin, a salt thereof, or an ester thereof contained in the composition (A), and the controlled release pharmaceutical composition has a ratio by mass of pitavastatin, a salt thereof, or an ester thereof contained in the composition (A) to pitavastatin, a salt thereof, or an ester thereof contained in the enteric composition (B) falling within a range of 1:1 to 1:40.

5. A controlled release pharmaceutical composition as described in claim 1, wherein the composition (A) releases in the stomach at least 60 mass % and less than 85

mass % pitavastatin, a salt thereof, or an ester thereof contained in the composition (A), and the controlled release pharmaceutical composition has a ratio by mass of pitavastatin, a salt thereof, or an ester thereof contained in the composition (A) to pitavastatin, a salt thereof, or an ester thereof contained in the enteric composition (B) falling within a range of 15:1 to 1:30.

6. A controlled release pharmaceutical composition as described in claim 1, wherein the composition (A) releases in the stomach at least 30 mass % and less than 60 mass % pitavastatin, a salt thereof, or an ester thereof contained in the composition (B), and the controlled release pharmaceutical composition has a ratio by mass of pitavastatin, a salt thereof, or an ester thereof contained in the composition (A) to pitavastatin, a salt thereof, or an ester thereof contained in the enteric composition (B) falling within a range of 30:1 to 1:20.

7. A controlled release pharmaceutical composition as described in any one of claims 1 to 6, wherein the enteric composition (B) is obtained by coating pitavastatin, a salt thereof, or an ester thereof or a composition containing the same with a component which dissolves at a pH of 3 or higher or by mixing pitavastatin, a salt thereof, or an ester thereof with a component which dissolves at a pH of 3 or higher.

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